The Effect of Growth Hormone on Life Expectancy: Is Cancer an Issue?
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Let us not forget what we were taught in Medical School: **First, do no harm.** Our objectives for today will be:

- to review the relationship between growth hormone and life expectancy
- to review the goals of age management medicine
- to review the concept of successful aging, and
- to review the literature on growth hormone and cancer.

In September 2002, Butler published his review of research dating back to the 1930s demonstrating that caloric restriction extends life expectancy in experimental animals. Mutations that decrease production of insulin-like growth factor 1 was also shown to increase life expectancy in laboratory mammals. However, he found no convincing evidence that the currently available existing so-called "antiaging" remedies can slow aging o increase longevity in humans.

Interestingly enough, a year earlier, Stavrou had defined growth hormone deficiency as a clinical syndrome that occurs in patients with pituitary or hypothalamic disease. He stated that these patients present with relatively nonspecific constitutional symptoms including abnormal body composition. He noted that life expectancy was significantly decreased in hypopituitary patients with growth hormone deficiency. In fact, cardiovascular disease was found to be the most common cause of death. More importantly, treatment with growth hormone reversed the abnormalities in body composition.

This was consistent with Rosen and Bengtsson retrospective review from over a decade earlier. 333 consecutive patients with hypopituitarism had received routine replacement therapy except for growth hormone and yet their overall mortality was found to be higher than any corresponding age and sex match cohort.

They concluded, and rightly so, that life expectancy is shortened in patients with hypopituitarism. Growth hormone deficiency could be a factor in the increased mortality due to cardiovascular disease.

Büllow came to a similar conclusion several years later in his retrospective cohort study involving 344 patients who were status post neurosurgical intervention for pituitary tumor. Over the better part of 40 years, these patients received conventional hormone replacement but did not receive any growth hormone. It was noted that these patients had increased mortality due to cerebro vascular and cardiovascular disease.

Tomlinson followed up several years later by reviewing 1,014 patients from the United Kingdom with hypopituitarism over the course of 8 years and noted excess mortality due to cardiovascular, cerebral vascular and respiratory disease. With significant factors including age, sex, craniopharyngioma and untreated growth hormone deficiency.

In a 12-month prospective unblinded study, Colao studied 30 growth hormone deficient patients and compared them to 30 normal patients. Of the 30 with growth hormone deficiency, 15 agreed to growth hormone. At study entry, growth hormone deficiency was associated with

significantly worse or lower IGF-1, lipid profile and cardiac parameters than their normal controls.

After 12 months of growth hormone supplementation IGF-1 had normalized, HDL had increased, total and LDL-C had decreased, and cardiac parameters had improved or normalized in all those who had received growth hormone. For those who did not receive any growth hormone, IGF-1 was stable but low, HDL had actually decreased; while total and LDL-Cholesterol had increased, and cardiac parameters had further worsened.

Besson a year later reported on the findings of a rather unique and large family in which 11 subjects had hereditary dwarfism and a genetic defect leading to isolated growth hormone deficiency. More specifically these 11 subjects were never treated for their growth hormone deficiency. Besson then compared their lifespan and cause of death directly to their unaffected brothers and sisters who totaled 25 as well as with the normal population of 100 men and women. He noted that the median lifespan in the growth hormone deficient group was significantly shorter than that of the unaffected brothers and sisters. He concluded that growth hormone treatment in adult patients suffering from either childhood or adult-onset growth hormone deficiency is crucially important.

We will now review the goals of age management medicine. While we may not be able to increase life expectancy or lifespan, we can certainly improve health span for quality of life.

So, what is age management medicine? Is preventive medicine focused on nutrition, exercise and hormone optimization. It's focused on the individual and on the individual's health rather than on public health. Age management medicine maximizes health span by minimizing risk of premature demise due to coronary artery disease, cancer, diabetes, osteoporosis and Alzheimer's disease.

Isley described the syndrome of growth hormone deficiency as comprised of weight gain, abnormal body composition with increased fat mass and decreased lean body mass, decreased bone mass, atherogenic lipid profile and increased cardiovascular risk. Isley noted that several retrospective studies using age matched control data suggesting increased mortality in patients with hypopituitarism, particularly from cardiovascular mortality.

Isley noted that the excess atherosclerotic cardiovascular disease was caused by components of the metabolic syndrome, including an abnormal accumulation of body fat resulting in central obesity, a decrease in insulin sensitivity and resulting dyslipedimia. The growth hormone deficiency paradigm poses that growth hormone deficiency leads to central obesity which leads to atherogenic, metabolic and inflammatory abnormalities which leads to excess cardiovascular disease which then leads to premature death.

An alternative paradigm poses that the chronically ill state can lead to central obesity as can unphysiological hormone replacement, as can caloric excess with or without activity deficit. The central obesity will then lead to estrogenic, metabolic and inflammatory abnormalities which will then lead to premature death. Isley concluded that treatment with growth hormone has proven benefits with regard to body composition, surrogate markers for cardiovascular disease and for bone health.

The 13 studies reviewed included a patient population ranging from 9 up to 68 for a duration of 6 months to 18 months with variable dosage. However, the effects were consistent in terms of an increase in lean body mass and decrease in fat mass. No changes were noted with regard to triglycerides levels, whereas there was a tendency to show improvement in HDL as well as LDL.

With all this in mind, Isley compared the annual cost data for growth hormone versus a typical statin, ACE inhibitor, and bisphosphonate. Not surprisingly growth hormone proved to be the most expensive by far.

In a randomized single blind, placebo-controlled trial in 40 men with adult growth hormone deficiency, Sesmilo showed that over 18 months growth hormone replacement reduced the levels of inflammatory cardiovascular risk markers, including central fat, lipoprotein(a), and glucose levels. He found no effect on lipoprotein levels.

In his review, Shimon posited that adult growth hormone deficiency is a characteristic clinical syndrome associated with an array of body composition alterations and metabolic abnormalities that impaired physical performance and psychological well-being. Growth hormone replacement in this population, he concluded, has resulted in considerable clinical benefits.

Blum analyzed the scores of 957 adults with growth hormone deficiency who completed the Question on Life Satisfaction Hypopituitarism Module as an assessment of quality of life for patients with hypopituitarism. He noted that the scores were significantly decreased at baseline and were almost normalized after 68 months of growth hormone therapy.

In a small but short study, Ljunghall evaluated 12 men with osteoporosis and found that plasma concentrations of IGF-1 were significantly lower than in healthy subjects. Bone mineral densities in spine, femoral neck and forearm were also significantly different between the patients and their controls. In the 3 men who elected to receive a five-day course of growth hormone, Ljunghall was able to demonstrate a significant increase in plasma IGF-1 as well as several biochemical indices of bone turnover. Specifically, serum bone-specific alkaline phosphatase and urinary calcium excretion. As I mentioned, this is a rather small and short study.

In Ghiron's review several years later, he concluded that low-dose IGF-1 may directly increase osteoblastic function with minimal increase in bone resorption and, therefore, IGF-1 may provide useful means to increase bone mass.

In an extension of an earlier 9-month trial, 33 of 36 patients elected to continue growth hormone therapy for up to 45 months.

Johansson adjusted the dose of growth hormone according to its side effects and, to maintain serum IGF-1 levels within physiologic range. Johansson was able to show that growth hormone treatment continued to have an effect on bone metabolism and bone mass for up to 45 months of therapy. Interestingly enough, changes in bone mass were greater in men, although they received a lower dose of growth hormone than women. Johansson then concluded that sensitivity to growth hormone in adult patients with growth hormone deficiency is gender dependent.

In 2001, Wuster analyzed Pharmacy and Upjohn International Metabolic Database; that goes by the acronym KIMS. He found 2,084 adult hypopituitarism patients with growth

hormone deficiency and analyzing compared their data with a controlled population of 1,176 individuals from the European Vertebral Osteoporosis Study. This was the first large-scale analysis to support the hypothesis of increased fracture risk in adult patients with hypopituitarism and growth hormone deficiency. He concluded that the increased risk appears to be attributable to growth hormone deficiency alone rather than to the other pituitary hormone deficiencies or to their replacement therapy.

In a nice review, Rosen and Rackoff concluded that clinical trials provide evidence that IGF-1 acts by increasing birth rate of remodeling osteons thus promoting bone resorption information. They further concluded that data supports that IGF-1 directly increases osteoblastic function with only a minimal increase in bone resorption.

Gotherstrom studied 118 adults with growth hormone deficiency. Five years of growth hormone therapy was noted to be safe and well tolerated and the effects on body composition, bone mass and metabolic indices were sustained. Specifically, Gotherstrom noted a sustained increase in lean body mass, a decrease in body fat, and an increase in total body bone mineral content at the lumbar as well as the femoral neck. In fact, at study end, bone mineral density in both lumbar spine and femoral neck were normalized. During the same period of time, total cholesterol and LDL cholesterol decreased, and HDL cholesterol increased.

At the end of five years, serum concentrations of triglycerides and hemoglobin A1c were found to be reduced compared to baseline values. And all of this speaks to the tremendous safety and efficacy of growth hormone therapy.

In a 5-year study of growth hormone replacement therapy in adults with adult-onset growth hormone deficiency, Svensson was able to demonstrate normalized isometric and isokinetic knee flexor and extensor strength. In this study, 109 consecutive adults were included. The mean initial growth hormone dose was 0.88 mg per day. The dose was gradually lowered and after five years the mean dose was 0.46 mg per day. The mean IGF-1 standard deviation score increased from -1.54 baseline to 1.53 at study end. Svensson also noted a sustained increase in lean body mass and decrease in body fat.

In yet another long-term trial of growth hormone therapy in growth hormone deficient adults, Gibney looked at 21 growth hormone deficient adults who originally took part in a randomized, double-blind, placebo-controlled trial of growth hormone treatment back in 1987. After completion of that trial, half the patients elected to receive continuous growth hormone replacement for subsequent 10 years, whereas 11 did not. After 10 years of growth hormone therapy, Gibney found an increase in lean body mass, an increase in muscle mass, an improvement in the atherogenetic lipid profile, a reduction in carotid intima media thickness and improvement in psychological well-being. No side effects were found that could not be accounted for, nor resolved with the reduction or adjustment in growth hormone dosing.

In a prospective study in healthy elderly individuals, Kalmijn sampled 186 participants from the population-based Rotterdam study age 55 to 80 years old. At baseline, fasting blood levels of IGF-1 and IGFBP-3 were obtained. A 30-point Mini Mental State Examination was also performed. Declined in cognition was found to be inversely related to serum IGF-1 levels along

with IGF-1 to IGFBP-3 ratio. A higher total IGF-1 along with higher IGF-1 to IGFBP-3 ratio was associated with less cognitive decline.

In a nice review, Lamberts concluded that in healthy elderly men serum IGF-1 levels have been demonstrated to be significantly associated with several aspects of cognition, specifically, speed of information processing.

Next, let's review the concept of successful aging. The concept of successful aging is akin to that of pornography as delineated by the Supreme Court, in other words: "you know it when you see it." Havighurst in 1961, described successful aging as "adding life to the years" and "getting satisfaction from life." In 1987, Row and Kahn described multiple physiological and psychosocial variables. The MacArthur studies looked at outcomes pertaining to physical performance and other indicators of functional status.

In 1982, Ryff described successful aging as a positive or ideal functioning related to development to work over a life course. Ten years later, Fisher interviewed 19 senior center participants aged 62 to 85 who described strategies for coping as their ideology for successful aging.

Gibson in 1995 referred to successful aging as reaching one's potential and arriving at a level of physical, social and psychological well-being in old age that is pleasing to both self and others. Palmore that same year in the *Encyclopedia of Aging* describes successful aging as that which would combine survival, health and life satisfaction. In other words, longevity, lack of disability and happiness.

Finally let's review the literature on growth hormone and cancer. In August 2002, Isley concluded in the annals of internal medicine that there does not appear to be an increase in the rate of cancer in adult patients who have received growth hormone therapy. What's more interesting about this statement is that it is part of a three-paper commentary that was published regarding the use of growth hormone therapy in adults with growth hormone deficiency. More specifically, Isley's perspective was that against the use of growth hormone therapy.

In Furstenberg's review published in May 2002, he acknowledged that IGF-1 is a major mediator of the effects of growth hormone and that there is a strong influence on cell proliferation and differentiation and that, in fact, it is a potent inhibitor of apoptosis. On the other hand, IGF binding proteins have independent effects on cell growth with IGFBP-3 having pro-apoptotic activities.

In Ma at al's prospective case control study, that was nested in the physicians health study, they analyzed the data from 14,916 men without diagnosed cancer. They acknowledged prior that IGF levels have not been statistically associated with cancer risk. After the analysis, it appeared that a combination of high IGF-1 and low IGFBP-3 appears to be related to a heightened risk. After controlling for IGFBP-3, age, smoking, body mass index and alcohol intake, men in the highest quartile for IGF-1 had an increased risk of colorectal cancer compared to men in the lowest quintile. On the other hand, after controlling for IGF-1 and other covariants, men with a higher IGFBP-3 had a lower risk. Because growth hormone positively influences production of both peptides, this casts doubt on its role as a driving force in the IGF cancer relationship.

In a very nice review published in September 2000, Yu and Rohan concluded that the

incident like growth factor family has a role in cancer as supported by epidemiologic studies. Specifically high levels of circulating IGF-1 and low levels of IGFBP-3 have been associated with increased risk of several common cancers; especially prostate, breast, colorectal and lung.

In June 1999, Abs et al evaluated KIMS, the Pharmacy and Upjohn International Metabolic Database which is a long-term open outcomes research program of hypopituitary adult patients with growth hormone deficiency who were treated in a conventional clinical setting. This particular analysis encompassed data from 1,034 hypopituitary patients who were treated for growth hormone deficiency for a total of 818 patients treatment years. No increased incidence of cancer was found among the growth hormone recipients.

In response to a trial in which severely ill patients were treated in an intensive care unit with either 16 or 24 units of growth hormone daily; the results of which showed an increase in mortality. Bengtsson et al in November 1999 analyzed KIMS yet another time. This time they looked at 1,903 patients who were treated for 2,334 patient treatment years. They concluded that growth hormone replacement therapy is not associated with any increase in mortality.

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